Public Health Genomics at the National Center on Birth Defects and Developmental Disabilities

Top Priorities

The National Center on Birth Defects and Developmental Disabilities (NCBDDD) has four main priorities related to genetics activities:

- Investigate susceptibility genes for birth defects
- Support, develop, and evaluate newborn screening programs for genetic disorders
- Improve quality of life of children with potentially disabling single gene disorders and their families
- Prevent morbidity and mortality related to genetic disorders of hemostasis by:
    - Investigating susceptibility genes for thrombotic diseases
    - Characterizing the types of health care services needed to care for people with thrombotic disease
    - Investigating the role of genetic mutations on development of inhibitors in hemophilia

Birth Defects Research
Birth defects etiologic research is a major and well-established NCBDDD activity. Numerous investigations are ongoing, but the most genomic-related project is the National Birth Defects Prevention Study (NBDPS). In 1996, Congress directed CDC to establish the Centers for Birth Defects Research and Prevention. This directive was formalized with the passage of the Birth Defects Prevention Act of 1998. Currently, NCBDDD has established centers in Arkansas, California, Iowa, Massachusetts, New York, North Carolina, Texas, and Utah. The centers were established in states with existing birth defect programs that had nationally recognized expertise in birth defects surveillance and research. Each of these centers is a site for the NBDPS. CDC coordinates the centers and participates in the NBDPS as the ninth study site.

The NBDPS has three components: review and classification of records of infants with birth defects by clinical geneticists, maternal interviews of eligible participants, and collection and processing of cheek swabs from study participants and their parents. Genomic DNA from buccal cells is stored both at the individual centers and at a central repository at CDC. The information gathered from the interviews, combined with the availability of DNA, provides an invaluable resource for the study of genetic susceptibility to environmental exposures for a broad range of carefully classified birth defects. The unprecedented statistical power from this collaborative study has enabled investigators to study the epidemiology and genetics of both common and rare birth defects, and the compiled data and banked DNA will facilitate future research as new hypotheses and improved technologies emerge.

Newborn Screening for Genetic Conditions
The first newborn screening program was implemented in the 1960s to provide early diagnosis of phenylketonuria (PKU). This early diagnosis allows dietary management as a means to prevent the development of mental retardation in children with PKU. While all states now screen universally for three disorders (PKU, galactosemia, and congenital hypothyroidism), considerable variation still exists in testing for other conditions. States also differ in specific laboratory techniques, storage and use of residual blood spots, and follow-up and integration of screening practices. The newborn screening system involves more than laboratory analysis, and recently a multiagency Newborn Screening Task Force has called for recognition of the

newborn screening system as a comprehensive public health program that includes screening, short-term and long-term follow-up, diagnosis, management, and evaluation. New technologies introduced in recent years have also led to interest in expert guidance and new funding for newborn screening.

Children with Potentially Disabling Single Gene Disorders
Pediatric single gene disorders account for about 13% of inpatients in pediatric hospitals, and for about 3% to 5% of pediatric deaths. Individually, single gene disorders are rare and often get "lost" in the overall picture. In addition to health and disability concerns, genetic conditions raise additional psychosocial and familial issues. Families, health care providers, and public health officials need to become familiar with the unique challenges raised by genetic conditions. Lessons learned from public health activities in single gene disorders can be applied to complex disorders as they become elucidated. The goals of NCBDDD are to:

- Develop surveillance systems that meet challenges of single gene disorders and that are expandable. Data from surveillance systems are necessary to determine the following:
    - How common is the condition?
    - Is it equally common in different racial and ethnic groups?
    - What is the natural history of the condition?
    - What factors affect disease progression?
    - Does the type of care received affect the progression?
    - Do different populations receive different care?
    - What services are families receiving?
    - What barriers to services are families facing?
- Improve screening and diagnosis.
- Improve services to patients and families.

Duchenne/Becker Muscular Dystrophy (DBMD): DBMD is the first disorder to be investigated using this approach. Duchenne muscular dystrophy (DMD) affects about 1 in 4,000 males and is the most common form of muscular dystrophy in children. In the absence of newborn screening, DMD is usually diagnosed when a boy is 3 to 6 years of age. Early signs include failure to walk by 18 months of age, frequent falling, difficulty getting up from a sitting or lying position, and a waddling gait. As muscle deterioration progresses, children with DMD become unable to walk around age 12 years. The disease is fatal in the teens or early 20s, because of severe respiratory and heart problems. A milder form of the disease, Becker muscular dystrophy, is caused by mutations in the same gene. The combined spectrum is referred to as Duchenne/Becker muscular dystrophy (DBMD). Standard birth defects monitoring systems in the United States do not detect children with DBMD because these children do not have recognizable signs or symptoms at birth. Consequently, existing birth defects monitoring systems would need to be supplemented with additional ascertainment sources to find all cases of DBMD. NCBDDD is working with four states to set up DBMD surveillance systems called the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet). The states are Arizona, Colorado, Iowa, and western New York state. The goal of the project is to find all patients with DBMD in the areas and collect information about them from their medical records. Because many patients with DBMD are seen in Muscular Dystrophy Association (MDA) clinics, the researchers are working closely with the MDA clinics in their states. In addition, the MD STARnet researchers will be searching for patients with DBMD through other neuromuscular clinics, emergency rooms, pathology laboratories, orthopedists, and muscular dystrophy associations to ensure that all patients with DBMD are included in the project. The states have worked together to develop a common system to find patients and collect information. Families that are identified in these areas will be contacted yearly to collect up-to-date information. NCBDDD is also sponsoring projects to identify the service needs of families with DBMD, pilot newborn screening for DMD, pilot infant screening for DMD, and identify cardiac care issues in carrier females.

Thrombotic Diseases
Hereditary defects in one or more of the clotting factors in blood can cause the formation of potentially dangerous blood clots (thrombosis). Approximately 5% to 8% of the U.S. population has one of these clotting disorders, collectively called *thrombophilia*. Thrombophilia is a propensity for blood clotting in which a genetic defect can be identified that often results in thrombosis. More than 60,000 Americans die each year from venous thromboembolism, the blockage of a blood vessel caused by a clot dislodged from a vein; in addition, nearly half of patients with deep vein clots experience long-term health consequences that adversely affect their quality of life. Evidence suggests that thrombophilia is related to adverse pregnancy outcome, including thrombosis in pregnancy and potentially recurrent fetal loss, intrauterine growth restriction of the fetus, and preterm delivery. A coordinated, standard approach to managing the care of these patients has not been established among health care providers.

Despite the substantial percentage of people with clotting disorders, thrombophilia is not easily recognized. Identifying the predisposing genetic risk factors and interacting external or environmental factors could help determine which people are most susceptible to clotting and help prevent the resulting complications. Moreover, identifying and understanding the modifiable risk factors associated with the risk of thrombotic disease will facilitate preventions and intervention efforts.

Hemophilia
Hemophilia is an inherited bleeding disorder that affects approximately 18,000 people (primarily males) in the United States. The disorder results from deficiencies in blood clotting factors and can lead to spontaneous internal bleeding and bleeding following injuries or surgery. These bleeding episodes can cause severe joint damage; neurological damage; damage to other organ systems involved in the hemorrhage; and, in rare cases, death. Treating the bleeding episodes involves the prompt and proper use of clotting factor concentrates.

As many as one-third of people with hemophilia will develop an antibody (inhibitor) to the intravenous antihemophilic factor products that are infused to stop or prevent a bleeding episode. Although most of these inhibitors are transient and will resolve, about 5% to 7% of the hemophilia population have a clinically significant long-term inhibitor. An inhibitor renders the treatment product ineffective in controlling bleeding. The public health costs associated with inhibitors are staggering. People with hemophilia with inhibitors are twice as likely to be hospitalized for a bleeding complication. In addition, the cost of hospital care for a bleeding complication is an average of 10 times greater for those with inhibitors compared with those without an inhibitor. Incidence rates of inhibitors appear to vary according to the defect on the Factor VIII or IX gene. However, less than 7% of people with hemophilia enrolled in Universal Data Collection (hemophilia surveillance) have undergone an analysis of their genetic defect, primarily due to the high cost and lack of insurance reimbursement.

Major 2004 Accomplishments of NCBDDD Programs in Genetics

National Birth Defects Prevention Study (NBDPS) Biologics Summit and Epidemiologic Findings
After 5 years of data collection, in 2003 and 2004 sufficient power was achieved for several NBDPS birth defect groups to allow epidemiologic analyses to begin. In 2004, data were published in the *Morbidity and Mortality Weekly Report* in response to a public health concern, raised by a scientific study showing a possible association between the drug loratadine, also sold under the brand name Claritin® and recently approved for over-the-counter use, and a male genital defect (hypospadias). The study showed no association between use of loratadine in early pregnancy and the occurrence of hypospadias. This study did not examine genetic risk factors for hypospadias because of the specific concern about a medication

exposure, but numerous other proposals for molecular analyses have been made to the NBDPS Data Sharing Committee. In April 2004, a Biologics Summit was held in Atlanta, Georgia to discuss strategies for optimal use of collected DNA. Speakers from NBDPS centers and other institutions discussed cutting-edge techniques such as whole genome amplification, high-throughput genotyping, and haplotype analyses. Immediate, practical solutions to improve sample collection and DNA yields were also proposed. Pilot testing of some of these suggestions has been instituted as a result of this meeting.

Cystic Fibrosis Screening Recommendations
NCBDDD convened a workshop on newborn screening for cystic fibrosis (CF) in Atlanta, Georgia, in November 2003, cosponsored by the Cystic Fibrosis Foundation. The workshop brought together national and international experts and state health department staff to review evidence of benefits and harms of such screening. Presentations from the workshop will be published in a special issue of the *Journal of Pediatrics* in 2005. A writing group of seven people conducted an evidence review of relevant studies and prepared an *MMWR Recommendations and Reports* that was published on October 15, 2004. The main recommendation from that review was that, based on evidence of moderate benefit and low risk of harm, states should consider adding CF to screening panels.

Colorado Project for Tracking Affected Children Identified Through Newborn Screening and Collecting Data Relating to a Variety of Long-Term Outcomes
Through an NCBDDD cooperative agreement with the Colorado Department of Public Health and Environment, this project will provide aggregate data relating to surveillance, short-term management, and long-term follow-up of infants with metabolic conditions and hemoglobinopathies identified through newborn screening. The primary objectives for the Colorado health department have been to integrate data from newborn blood spot and hearing screenings and to ascertain information from specialty clinics for children with hemoglobinopathies, metabolic disorders, and other conditions identified by newborn screening. Data collection using a health department-developed electronic instrument in specialty clinics began in 2004, with plans to integrate data in the upcoming year.

Storage and Use of Residual Dried Blood Spots From State Newborn Screening Programs
Residual blood spot specimens have historically been used for quality control and evaluation of new screening tests and clinical or forensic testing. In recent years, numerous investigators have also used these stored blood spots for a variety of other purposes. The number and visibility of these types of studies have increased the awareness of the uses of stored blood spots among researchers, public health officials, ethicists, and policymakers. In 2004, investigators from NCBDDD collaborated with the Office of Genomics and Disease Prevention, the National Center for Environmental Health, and the Association of Public Health Laboratories to compile and present 2003 survey data regarding state practices on storage and use of blood spots.

Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet) Implementation
Data collection for this project began in April 2004. Families who are identified through the MD STARnet system will be asked to take part in interviews with public health workers to provide information related to DBMD that might not be found in the medical records. The types of information that will be collected include basic demographic information (such as race and ethnicity), the types of treatments that have been received, the types of clinics that the care was received in, and any medical problems associated with DBMD.

Newborn Screening for Duchenne Muscular Dystrophy (DMD) Workgroup
On March 12, 2004, NCBDDD sponsored a one-day meeting in Atlanta, Georgia, with experts from around the world to look at newborn screening for DMD. At the meeting, past and

present DMD newborn screening programs were discussed, as well as known and potential risks and benefits of such programs. A report for the general public was released in September 2004 (http://www.cdc.gov/ncbddd/duchenne/NBS_Lay_Report.pdf). A second report will be submitted for publication in a peer-reviewed journal. Highlights from the meeting were presented at the 2nd National NCBDDD Conference in July 2004.

Long-Term Follow-Up of Children with Metabolic Disorders Identified Through Tandem Mass Spectrometry-Based Newborn Screening
Newborn screening programs have traditionally been limited to conditions that are serious, treatable or controllable, and with a natural history that is understood. In the 1990s, the technology of tandem mass spectrometry was introduced for population-based newborn screening. This technology allows for a more accurate measurement of metabolites associated with a broader range of conditions than was previously available. For some conditions, such as phenylketonuria, the benefits of newborn screening and early treatment are generally accepted. However, for other conditions, such as some of the fatty acid oxidation disorders, evidence regarding long-term benefit from screening and intervention is lacking. For certain fatty acid oxidation disorders, there is also currently a lack of data regarding the distinction between pathologic levels of some metabolites and natural variations in levels. Population-based tracking and follow-up studies of children identified through tandem mass spectrometry are needed to assess the public health impact of newborn screening for many of the disorders identified with this technology. In 2004, an electronic system was developed and tested to collect and pool data on children in Idaho, Iowa, and Oregon with selected metabolic disorders. The data collected include collection of information related to treatment options, treatment compliance, and long-term outcomes.

Ongoing Initiatives Related to Genetic Disorders of Hemostasis
The Division of Hereditary Blood Disorders (DHBD), NCBDDD, is collaborating with several academic institutions to conduct case-control studies investigating the association of gene polymorphisms with thrombotic outcomes, evaluating health-related services directed toward the reduction or prevention of complications of thrombosis and thrombophilia, and investigating inhibitor development in people with hemophilia.

The Role of the Maternal Hemostatic System and Maternal Coagulation Genes in Intrauterine Growth Restriction
Disruption of uteroplacental circulation resulting in decreased nutrient exchange between mother and fetus has been implicated as a potential cause of intrauterine growth restriction (IUGR). The DHBD, NCBDDD, is conducting a multisite case-control study to evaluate the presence and interaction of genetic polymorphisms of the coagulation, fibrinolytic, and inflammatory pathways and their association with IUGR. Study enrollment began in February 2000 and is expected to continue through 2005. DNA samples are being collected from both mother and fetus to assess the role of both the maternal and fetal hemostatic systems in IUGR. Findings from this research will help to further elucidate the role of these genes and pathways in IUGR pathophysiology. Results might also help to identify women and fetuses most at risk for IUGR and to develop targeted preconception care, as well as management for IUGR pregnancies.

The Genetic Attributes and Thrombosis Epidemiology (GATE) Study
The GATE study is a case-control study to evaluate the genetic and environmental risk factors for venous thromboembolism (VTE). Current analyses have focused on associations between VTE and polymorphisms in coagulation, fibrinolytic, and inflammatory pathways. Early analyses have been published in the scientific literature and presented at international meetings. Findings from this research will help to elucidate the role of gene polymorphisms and

interactions with lifestyle factors in VTE pathophysiology. Results could also help to identify people at risk for VTE and to develop targeted preventive care.

Health Care Services for People With Thrombotic Disease
The Division of Hereditary Blood Disorders, NCBDDD, has cooperative agreements with eight Hemostasis and Thrombosis Centers (pilot sites) in the United States to provide health-related services, directed toward the reduction or prevention of complications of thrombosis, thrombophilia, and bleeding disorders. The initial objectives of this collaboration are to characterize the patients treated at pilot Hemostasis and Thrombosis Centers and the types of services provided. To achieve these goals, a Web-based data registry has been created and implemented at the pilot sites. Through the registry, information is collected for the purposes of: (1) determining the demographics of the patient population; (2) characterizing referral patterns to the centers; (3) elucidating the experiences of the patients at the centers (extent of care, encounters with health care professionals, and educational materials received); (4) describing the medical history of these patients, laboratory and radiological tests performed, and treatment prescribed; and 5) investigating and characterizing use of the center through follow-up and return visits. Since August 2003, 895 patients have been enrolled in the registry. Long-term goals are to evaluate the effectiveness of an integrated health care model in preventing and treating coagulation disorders and their complications. Data collection across pilot sites will facilitate future collaborative clinical and epidemiologic investigations, health services evaluations, and quality of life assessments.

Inhibitors and Hemophilia
Beginning in 2005, DHBD will begin a pilot study to perform post-marketing surveillance of treatment products for inhibitors as part of an ongoing surveillance project already established in the bleeding disorders community. Hemophilia genetic testing is important to the success of this study for several reasons. First, hypotheses concerning the risk for inhibitor development and specific genetic defects can be tested. Second, the possible confounding effects of certain genetic defects on product-specific risk can be assessed. Third, should the results of the study confirm that patients with certain defects are at higher risk of inhibitors, interventions designed to minimize this risk can be developed and tested. For the study, mutations in FVIII will be detected by direct nucleotide sequencing. In the first year of the study, genetic sequencing will be performed on 500 patients.

Future Directions

Based on the four main priorities outlined in the introduction, investigators at the National Center on Birth Defects and Developmental Disabilities and NCBDDD grantees have specific goals for future activities:

Investigate Susceptibility Genes for Birth Defects

- Begin analyses of National Birth Defects Prevention Study biologic data to investigate for gene–environment and gene–gene interactions in the causation of specific birth defects.
- Initiate alternative and novel procedures to improve collection of biologic samples from NBDPS participants.
- Determine strategies for optimal analyses of collected NBDPS samples through a genetic analysis working group.

Support, Develop, and Evaluate Newborn Screening Programs for Genetic Disorders

- Support existing and new efforts to link newborn screening records with postnatal data sources, such as clinic treatment records, to ensure optimal outcomes.

- Study the risks and benefits of newborn and other early screening programs for conditions that do not meet the traditional criteria for newborn screening in the United States.
- Enhance long-term evaluation of children identified through tandem mass spectrometry-based newborn screening by increasing the number of states participating in long-term follow-up studies.
- Conduct economic evaluations of newborn screening tests.

Improve Quality of Life of Children with Potentially Disabling Single Gene Disorders and Their Families

- Identify preventable risk factors for secondary complications.
- Decrease age of diagnosis.
- Improve health care and related services for families.
- Decrease barriers to health care and related services.

Prevent Morbidity and Mortality Related to Genetic Disorders of Hemostasis

- Complete, analyze, and disseminate results from case-control studies in the Division of Hereditary Blood Disorders, NCBDDD. Determine risk factors and describe potential intervention measures.
- Evaluate the effectiveness of the specialized health care system to improve health outcomes and quality-of-life measures for people with thrombophilia.
- Develop hereditary blood disorder educational materials for patients and health care providers.
- Develop rapid screening methods to detect risk factors for thrombosis.
- Extend genetic testing for people with hemophilia and inhibitors.